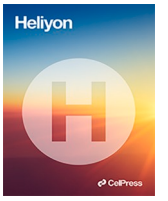
Heliyon 10 (2024) e25567

Contents lists available at ScienceDirect

Heliyon

journal homepage: www.cell.com/heliyon



Research article

Endovascular electroencephalography (eEEG) can detect the laterality of epileptogenic foci as accurately as subdural electrodes

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ARTICLE INFO

Keywords:
Animal model
eEEG
Lateralization
Penicillin
Epileptogenicity
Micro-catheter

ABSTRACT

Background: Traditional brain activity monitoring via scalp electroencephalography (EEG) offers limited resolution and is susceptible to artifacts. Endovascular electroencephalography (eEEG) emerged in the 1990s. Despite early successes and potential for detecting epileptiform activity, eEEG has remained clinically unutilized. This study aimed to further test the capabilities of eEEG in detecting lateralized epileptic discharges in animal models. We hypothesized that eEEG would be able to detect lateralization. The purpose of this study was to measure epileptiform discharges with eEEG in animal models with lateralization in epileptogenicity.

Materials and methods: We inserted eEEG electrodes into the transverse sinuses of three pigs, and subdural electrodes (SDs) on the surfaces of the left and right hemispheres. We induced epileptogenicity with penicillin in the left brain of pigs F00001 and F00003, and in the right brain of pig F00002. The resulting epileptiform discharges were measured by eEEG electrodes placed in the left and right transverse sinuses, and conducted comparisons with epileptiform discharges from SDs. We also had 12 neurological physicians interpret measurement results from eEEG alone and determine the side (left or right) of epileptogenicity.

Results: Three pigs were evaluated for epileptiform discharge detection using eEEG: F00001 (7 months old, 14.0 kg), F00002 (8 months old, 15.6 kg), and F00003 (8 months old, 14.4 kg). The eEEG readings were compared with results from SDs, showing significant alignment across all subjects ($p < 0.001$). The sensitivity and positive predictive values (PPV) were as follows: F00001 had 0.93 and 0.96, F00002 had 0.99 and 1.00, and F00003 had 0.98 and 0.99. Even though one of the neurological physicians got all sides incorrect, all other assessments were correct. Upon post-experimental dissection, no abnormalities were observed in the brain tissue or in the vascular damage at the site where the eEEG was placed, based on pathological evaluation.

Abbreviations: ARRIVE, Animal Research: Reporting of In Vivo Experiments; EEG, electroencephalography; eEEG, endovascular electroencephalography; fMRI, functional Magnetic Resonance Imaging; fNIRS, functional Near-Infrared Spectroscopy; GABA, gamma-aminobutyric acid; PET, Positron Emission Tomography; PPV, positive predictive value; SD, subdural electrode; SEEG, stereo-electroencephalography; SPECT, Single Photon Emission Computed Tomography.

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https://doi.org/10.1016/j.heliyon.2024.e25567
Received 5 July 2023; Received in revised form 28 December 2023; Accepted 29 January 2024
Available online 1 February 2024

Conclusion: With eEEG, lateralization can be determined with high sensitivity (>0.93) and PPV (>0.95) that appear equivalent to those of subdural EEG in the three pigs. This lateralization was also discernible by neurological physicians on visual inspection.

1. Introduction

The traditional method of monitoring brain activity has been through scalp electroencephalography (EEG), which involves placing electrodes on the surface of the scalp to record electrical signals from the brain. However, scalp EEG has limitations in terms of spatial resolution, susceptibility to artifacts, and an inability to detect direct brain activities because of tissues such as the scalp, hair, and calvaria.

The idea of endovascular EEG (eEEG) as a method of measuring brain activity from within blood vessels was developed in the 1990s [1,2]. This technology built on the pioneering work of invasive EEG techniques such as stereo-electroencephalography (SEEG) and depth electrodes, which involve surgically implanted electrodes for high-resolution monitoring of brain activity. However, these methods carried risks inherently associated with the invasive surgical processes involved and SEEG and depth electrode placement cannot be performed as easily as with non-invasive methods such as preoperative neuroimaging, scalp EEG, and long-term video EEG.

The development of eEEG technology represented a significant leap. Initial animal studies demonstrated the feasibility of eEEG for recording brain activity [3]. The primary breakthrough came when flexible stent-like electrodes were found to be insertable through blood vessels for positioning near areas of interest in the brain without needing invasive surgery. Stentrodes, as these electrodes came to be known, deliver high-quality EEG signals with increased spatial resolution and reduced susceptibility to artifacts [4]. However, while initial results were promising, eEEG faced substantial challenges, many of which were common to the process of developing novel biomedical technologies. Regulatory, technical, and clinical barriers all had to be overcome [5,6].

In clinical practice, we often observe that the lateralization of epileptic seizure symptoms is not clearly depicted in scalp EEG during either seizure or interictal periods. In addition, seizure semiology and scalp EEG findings sometimes appear diametrically opposed [7,8]. Comprehensive searches for the predicted epileptogenic zone are therefore undertaken using methods such as magnetoencephalography [9], EEG-fMRI (functional Magnetic Resonance Imaging) [10], fNIRS (functional Near-Infrared Spectroscopy)-EEG [11], SPECT (Single Photon Emission Computed Tomography) [12], and PET (Positron Emission Tomography) [13]. In cases of uncertainty about lateralization, judgments about lateralization, irritative zone, and seizure onset zone can be made by inserting intracranial electrodes on both sides [14]. However, the fact that 20 % of patients do not undergo epilepsy surgery, including focal resection, following intracranial electrode placement and instead have the electrodes removed [15,16], along with the risks of intracranial electrodes [17–20], makes invasive studies more difficult to perform compared to non-invasive tests due to the invasiveness. Recently, less-invasive SEEG has been becoming mainstream [21], but some risk of complications remains [22].

We have reported that eEEG can detect the epileptic discharges detected by subdural electrodes in experiments using a pig animal model [23]. The previous experiment [23] placed the eEEG electrode in the superior sagittal sinus, not allowing clarification of whether lateralization can be judged. As the experiment also demonstrated the potential high spatial resolution of eEEG, we hypothesized that eEEG might also be able to detect lateralization. As mentioned above, whether clinically [24–26] or neurophysiologically [27,28], laterality has long been emphasized and pursued in the treatment of epilepsy. Given that eEEG demonstrates laterality in this research, we believe that it will have a significant positive impact when applied clinically. Therefore, we have set the objectives of this research as follows. The purpose of this study was thus to measure epileptiform discharges with eEEG in animal models with lateralization of epileptogenesis and to make this lateralization explicit.

2. Methods

2.1. Study design

This was an observational study focusing on penicillin-induced epilepsy models in pigs. The design and analysis of this study were conducted in accordance with the ARRIVE (Animal Research: Reporting of In Vivo Experiments) guidelines version 2.0, originally published in *PLOS Biology* [29].

2.2. Setting and ethics approval

This study was performed at the Institutional Animal Care and Use Committee of Nihon Bioresearch Inc., Japan. The study adhered to the recommendations outlined in the Guide for the Care and Use of Laboratory Animals of the National Institutes of Health. Approval for the protocol was obtained from the Institutional Animal Care and Use Committee of Nihon Bioresearch Inc. (study no. 420219). Every possible measure was taken to minimize any potential suffering experienced by the three female domestic pigs (Gottingen miniature pig) used as subjects throughout the course of this study.

The objective of this study was to confirm whether the laterality of epileptiform discharges can be determined through eEEG in pigs, wherein epileptogenicity was induced in the brain of a single pig and eEEG electrodes were placed bilaterally. This investigation involves three pigs and did not involve the use of a control group.

2.3. Materials

2.3.1. Sample size and animal information

We used three female pigs in this experiment. The pigs used as subjects are rigorously managed from birth in terms of nutritional status, body weight, health, and other factors. In this experiment, given considerations such as the weight and the size of the brain, we believed that minimizing individual differences, such as reactions to penicillin and electrophysiological variations, would yield more accurate results. Consequently, taking into account gender, age at birth, and body weight, we decided to use female pigs exclusively. The demographics of the three target pigs are summarized in Table 1 (Table 1).

2.3.2. General anesthesia

Each pig underwent a 12-h fasting period prior to the initiation of general anesthesia. Intravenous administration of 1.5 mg/kg of midazolam (Dormicum®) and 15 mg/kg of ketamine (Ketalar®) was performed. Before tracheal intubation, thiopental (Pentothal®, 25 mg/mL) was administered. Following oral intubation, anesthesia maintenance was achieved through ventilation (7–8 L/min, 18 breaths/min) with 40 % oxygen in air and isoflurane. Periodic administration of pancuronium bromide (Pavulon®, 4 mg/h) was employed as a muscle relaxant [30–32].

2.3.3. eEEG

We developed a novel eEEG device using a nickel-titanium alloy wire coated with an electrically non-conductive polymer, along with a platinum alloy electrode. The device has a length of 3 mm and a diameter of 0.25 mm. This device is considerably thinner than conventional microcatheters typically used for accessing cerebral blood vessels, measuring only 0.010 inches in diameter. Furthermore, this microcatheter is compatible with guidewires, enhancing its versatility and usability (Fig. 1).

2.3.4. Placement of endovascular and subdural electrodes

After inducing general anesthesia, eEEG electrodes were placed in bilateral transverse sinuses from bilateral jugular vein access points. After the placement of eEEG electrodes in the transverse sinuses, craniotomy was performed. Local anesthesia using lidocaine was administered for the skin incision. Linear dural incisions of approximately 1.5 cm in length were made on both hemispheres. Subsequently, 4-contact strip array subdural electrodes (SD) (AD-Tech MedicaL; Owk, WI, USA) were placed on the surface of each hemisphere and secured to the peripheral regions of the dura mater [Fig. 2 (A-C)]. The distance between the centers of adjacent contacts was 1 cm.

For safety considerations and to assess complications, we conducted a pathological autopsy after the experiment to determine whether the eEEG placement had caused any vascular damage, and to check for cerebral hemorrhage or infarction.

2.3.5. Swine animal model of focal cortical epileptiform discharges

We conducted corticectomy (3 mm wide, 3 mm deep) in the left inferoposterior parietal area for F00001 and F00003, and in the right for F00002, followed by injection of 1.2 mg of benzyl-penicillin diluted with stock solution of 200 units/μL (total volume, 10 μL) into the corticectomy at a depth of 5 mm. when creating an epileptic focus with penicillin, among the subjects F00001-00003, it is necessary to create the focus on the opposite side for at least one pig compared to the other two. This was our rationale behind deciding the left or right side for the epileptic focus.

This procedure was performed to artificially induce epileptogenicity [33].

Penicillin is a widely used antibiotic that belongs to the beta-lactam class of antibiotics. While its primary purpose is to combat bacterial infections, this agent is also known to have proconvulsant properties and can induce epileptogenicity. The specific mechanism by which penicillin induces epileptiform activity is not completely understood, but is thought to involve several factors:

Excitatory Effects: Penicillin has been shown to enhance excitatory neurotransmission in the brain, increasing the release of excitatory neurotransmitters such as glutamate, and inhibiting reuptake of these neurotransmitters. This leads to an imbalance between inhibitory and excitatory neurotransmission, resulting in an increased propensity for epileptic activity [34].

GABA Inhibition: Penicillin can inhibit the activity of the inhibitory neurotransmitter gamma-aminobutyric acid (GABA). GABA normally dampens neuronal excitability by inhibiting the firing of neurons. When penicillin reduces the effectiveness of GABA, inhibitory control over neuronal activity is diminished, increasing the likelihood of epileptiform discharges [35].

2.4. Selection of epileptiform discharges

From F00001 to F00003, measurements of eEEG and SD were conducted under general anesthesia for 25–30 min. From our experience, discharges thought to be epileptiform discharges continue for several minutes immediately after penicillin injection, then

Table 1
Demographic and experimental Details of the pigs.

	Age	Sex	Bodyweight	Experimental Date
F00001	7months old	Female	14.0 kg	2023-04-16
F00002	8months old	Female	15.6 kg	2023-05-13
F00003	8months old	Female	14.4 kg	2023-05-14

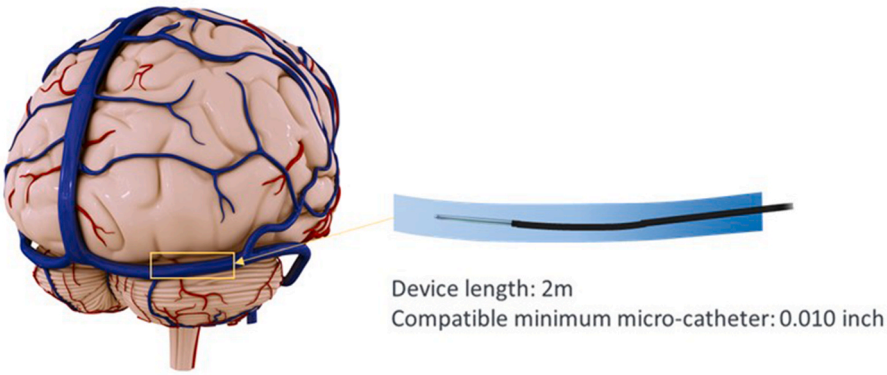

Fig. 1. On the left side of the figure, a human brain is used for easier understanding. In the right transverse sinus, the eEEG is placed using a micro-catheter. The eEEG has a total length of 2 m and approaches the blood vessels in the brain using a 0.001-inch micro-catheter.

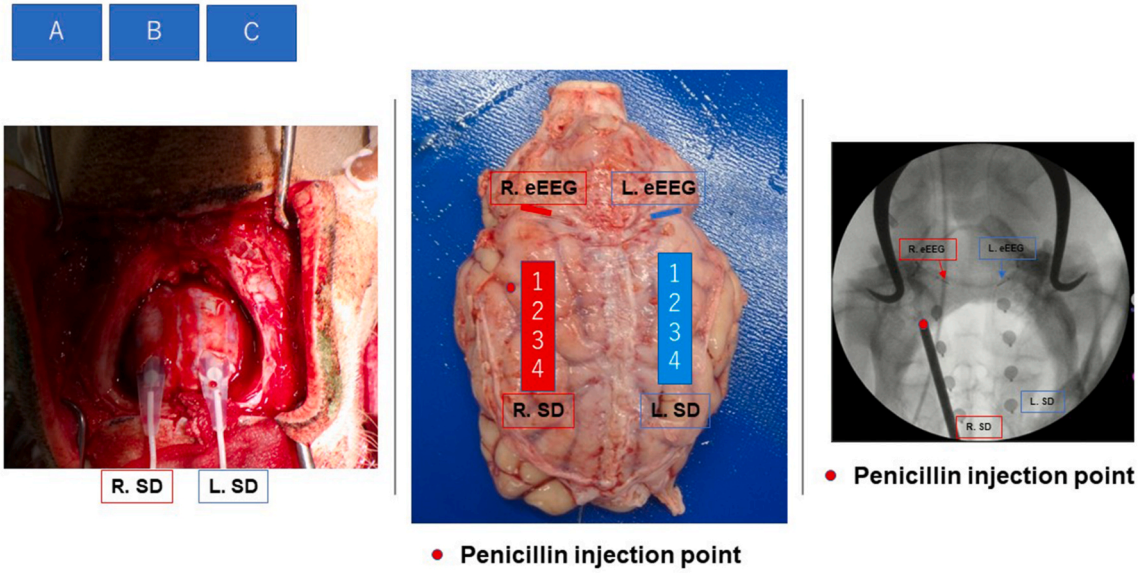

Fig. 2. Relationships between subdural electrodes, endovascular electroencephalography electrodes, and penicillin injection point (F00002)
After craniotomy, we placed subdural electrodes (SDs) in the left and right hemispheres (A). For clarity, we show the approximate placement of SDs and endovascular electroencephalography (eEEG) electrodes, and the location of the penicillin injection on an extracted pig brain (B). Actual positions of the SD, eEEG, and the site of penicillin injection are indicated on fluoroscopy images (C).

disappear and reappear about 5–8 min after injection, continuing for about 20 min. We therefore counted the discharges that appeared in the 5 min from 10 min after the injection of penicillin. Only the eEEG results of the above period were presented to the epileptologist (KH), without showing the results from SD. Circles were marked on what were thought to be epileptiform discharges, and triangles on questionable findings. The epileptologist (KH) performed the task based solely on EEG activities, without being informed of the penicillin injection side.

2.5. Outcome measurements

2.5.1. Primary outcome measurement

The results of the marking were counted by another epileptologist (AF), divided into discharges that matched with the SD on the penicillin injection side and discharges that did not. In cases where the initial observation did not match with the SD, or where the discharge of the SD could not necessarily be called an epileptiform discharge, and where the epileptologist (AF) had judged the initial observation of the eEEG to represent an epileptiform discharge based on morphology, the result was considered to be an epileptiform discharge that SD did not detect, but that eEEG did.

2.5.2. Secondary outcome measurement

Similarly, the 5-min span starting 10 min after penicillin injection was interpreted by the 12 neurological physicians (neurologists, pediatric neurologists and epilepsy neurosurgeons). Neurological physicians were told that penicillin had been injected into either the left or right side to create an epilepsy focus, and were asked to determine from the eEEG discharges alone which side was showing epileptic activity. During this, neurological physicians were asked to make judgments in three levels of "absolute", "probable", or "unclear".

2.5.3. Post-experimental dissection and pathological results

Upon post-experimental dissection, no abnormalities were observed in the brain tissue or in the vascular damage at the site where the eEEG was placed, based on pathological evaluation.

2.6. Bias

We believe that the discharges seen on eEEG measure epileptiform discharges [23,36], but at this point, there was no guarantee that the discharge from eEEG would represent an absolutely reliable epileptiform discharge. Therefore, relying solely on the eEEG discharge for judgment might introduce bias, as we have to reference the epileptiform discharges from the SD to judge the accuracy of epileptiform discharges.

Also, when having physicians interpret the data, the reading was made only based on the fact that penicillin was injected into one side to create epileptogenicity and that the eEEG electrodes were placed on both sides. This may have imposed psychological stress on physicians to indicate correctness, which could also have influenced responses.

2.7. Statistical analysis

The chi-square test was used for comparisons of the epileptiform discharges between SD and eEEG. We also assessed the sensitivity of eEEG to determine its ability to correctly identify those with epileptiform discharges. Additionally, the Positive Predictive Value (PPV) was computed to understand the probability that subjects identified by eEEG as having epileptiform discharges truly have them. Values of $p < 0.05$ were considered statistically significant. All analyses were conducted using Sigma Plot version 14.5 software (Systat Software, San Jose, CA, USA).

3. Results

3.1. Participants' demographics

Each pig was assigned an identification code, as follows (Table 1):
F00001: At the time of surgery, F00001 was 7 months old and weighed 14.0 kg.
F00002: At the time of surgery, F00002 was 8 months old and weighed 15.6 kg.
F00003: At the time of surgery, F00003 was 8 months old and weighed 14.4 kg.

3.2. Outcome measurements

3.2.1. Primary outcome

The results of scoring were divided into three patterns: 1) cases where an epileptiform discharge was judged to be present in the eEEG and marked as a circle matched with the SD; 2) cases where an epileptiform discharge was judged as doubtful in the eEEG and marked as a triangle matched with the SD; 3) cases where the SD did not detect epileptiform discharges or where the initial SD observation could not necessarily be described as an epileptiform discharge, but was considered an epileptiform discharge on eEEG. The results from F00001 to F00003 are summarized in a table (Table 1). All pigs showed results from eEEG significantly consistent with those from SD ($p < 0.001$ each). In other words, eEEG detected the side of penicillin injection equivalently to the SD. The sensitivity and positive predictive values (PPV) were 0.93 and 0.96 for F00001, 0.99 and 1.00 for F00002, and 0.98 and 0.99 for F00003, respectively (Table 2).

Table 2
Relationship between eEEG spikes and SD spikes.

	F00001		F00002		F00003	
	SD spike	SD non-spike	SD spike	SD non-spike	SD spike	SD non-spike
eEEG spike (marked as ○)	86	4	153	0	170	2
eEEG doubtful spike (marked as △)	6	0	1	0	3	0
Sensitivity	0.93		0.99		0.98	
Positive prospective value	0.96		1		0.99	

3.2.2. Representative epileptiform discharges

Fig. 3 presents a portion of eEEG and SD discharges from F00002. First, only the bottommost eEEG was interpreted without showing SD discharges, and circles were placed on what were thought to represent absolute epileptiform discharges. After that, the epileptiform discharge that matched with the simultaneously recorded SD discharges were considered correct.

3.2.3. Secondary outcomes

The neurological physicians determined laterality from each eEEG. In a three-level evaluation of "absolute", "probable", and "unclear", neurological physician #3 was correct when rating F00001 as probable. Of the 12 physicians, only one (physician #6) made a judgment contrary to the rest. Except for these two results, all other assessments were correctly identified as absolute (Table 3).

4. Discussion

4.1. Key results

The eEEG was able to determine lateralization with high sensitivity (>0.93) and PPV (>0.95) in the three pig epilepsy models. Neurological physicians were able to determine lateralization through visual inspection. Of the 12 physicians, only one made a judgment contrary to the rest. This physician argued that "Although the spikes are clearly localized on one side, slow-wave components are not observed on the side showing spikes, so I believe the epileptogenic focus is on the side without spikes."

Indeed, there is a perspective that focal slowing indicates an epileptogenic focus [37], but this might just be an over-reading due to the psychological pressure mentioned in the context of bias. In fact, almost all physicians expressed hesitation before answering, showing that it was so clear that they wondered if there was a catch.

In other words, we believe that if judgments can be made without bias, the aforementioned high sensitivity and PPV would be sufficient for making judgments on lateralization, enabling practical application.

4.2. The path to practical implementation

The idea of eEEG existed in the 1990s but has long remained clinically unutilized [1,2]. This can be attributed to significant barriers, including regulatory and economic aspects [5,6]. However, eEEG has been gaining more attention recently [36], likely influenced by the development of micro-catheters. The development of cerebral micro-catheters has greatly advanced the fields of neurosurgery and interventional radiology, allowing minimally invasive procedures and targeted treatments in the intricate blood vessels of the brain. Initially, older catheters were larger and less flexible, posing challenges in delicate maneuvers. However, the introduction of microcatheter guidewires has improved precision and safety by allowing the navigation of complex vessel networks [38]. Integration of imaging technologies has enabled real-time visualization, ensuring accurate catheter placement and reducing complications [39]. Overall, these developments have revolutionized neurovascular interventions, improving outcomes and patient care. While the present study did not address the safety of eEEG in humans, direct comparison with the risks of SD is not possible. However, considering that eEEG involves placing a device in a vein, and that it is a procedure that does not require opening the skull, it has the potential to be a device that can determine lateralization without being highly invasive. We will be verifying the safety of eEEG

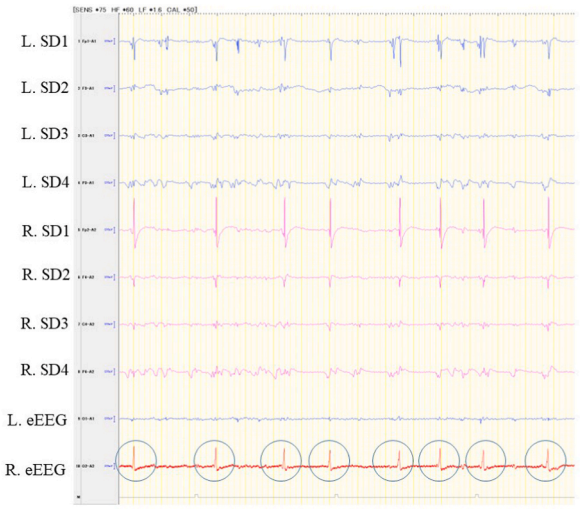

Fig. 3. Representatives of selected epileptiform discharges
Select epileptiform discharges from the endovascular electroencephalography and subdural electrodes (SDs) of F00002. Only eEEG discharges were initially interpreted, with circles marking suspected epileptiform discharges. Those matching concurrent SD discharges were deemed correct.

Table 3
Judgement of laterality by neurological physicians.

	Physician #1	Physician #2	Physician #3	Physician #4	Physician #5	Physician #6	Physician #7	Physician #8	Physician #9	Physician #10	Physician #11	Physician #12
F00001	absolutely left	absolutely left	probably left	absolutely left	absolutely left	absolutely right	absolutely left	absolutely left	absolutely left	absolutely left	absolutely left	absolutely left
F00002	absolutely right	absolutely right	absolutely right	absolutely right	absolutely right	absolutely left	absolutely right	absolutely right	absolutely right	absolutely right	absolutely right	absolutely right
F00003	absolutely left	absolutely left	absolutely left	absolutely left	absolutely left	absolutely right	absolutely left	absolutely left	absolutely left	absolutely left	absolutely left	absolutely left

Neurological physicians determined laterality from each eEEG. In a three-level evaluation of "absolute", "probable", and "unclear" findings, Physician #3 was correct when rating F00001 as probable. Only Physician #6 identified a penicillin-induced focus contralateral to the side of penicillin injection. Except for these, all other assessments were correctly identified as absolute.

in humans, along with its utility.

4.3. Potential usefulness of eEEG as inferred from this study

In cases where a lateral difference exists in seizure semiology, but no lateralization is indicated in other examinations, SEEG is currently considered the most viable option [40,41]. However, the current study suggests that lateralization can be determined as reliably with eEEG as with SD, suggesting potential for an increase in surgical eligibility among drug-resistant epilepsy cases that were previously deemed inoperable. Conversely, in cases where a focal onset can be predicted from imaging such as tuberous sclerosis complex, multiple cerebral cavernous angiomas, etc., but lateralization cannot be determined from seizure semiology or scalp EEG, eEEG may conceivably indicate lateralization. If the laterality can be determined using eEEG in cases of temporal lobe epilepsy where the laterality is unclear, the resection area for temporal lobe epilepsy is 'amygdala hippocampectomy with or without anterior temporal lobectomy.' This means it might be possible to proceed to treatment with only eEEG, potentially bypassing the need for SD or SEEG. In other words, it could become a less invasive diagnostic tool.

4.4. Limitations

At this point, the limitations of this study lie in the fact that we could only measure epileptiform discharges from eEEG electrodes placed in the superior sagittal sinus in previous experiments [23] and the transverse sinus in this one. Thus, we could not determine the extent of spatial resolution provided by eEEG. For future studies, placing multiple eEEG electrodes in various locations, such as the cavernous sinus, deep cerebral veins, and cortical veins, could help determine the level of spatial resolution achievable.

The sample size of this study was limited to only three female pigs, making it difficult to assert the strength and generalizability of the results. The authors also recognize the lack of a control group as a potential weakness in the scientific foundation of the study. In this research, based on the results of pathological dissection, no complications, including tissue damage from eEEG, were observed. However, it is essential to conduct further verification by increasing the number of subjects and considering its application in humans in the future.

5. Conclusion

Lateralization can be determined with high sensitivity (>0.93) and PPV (>0.95) by eEEG, offering equivalent results to those from SD. Lateralization was also discernible by neurological physicians on visual inspection.

Funding

This research was supported by the Japan Agency for Medical Research and Development (AMED) under grant number JP23he0122011.

Institutional review board statement

This research adhered strictly to the protocols outlined in the Guide for the Care and Use of Laboratory Animals as provided by the National Institutes of Health. All experimental procedures were sanctioned by the Institutional Animal Care and Use Committee of Nihon Bioresearch Inc. (study no. 420219). We exerted every effort to minimize distress for the female domestic pigs (Gottingen miniature pig) employed in our study.

Informed consent statement

Not available for this study.

Additional information

No additional information is available for this paper.

CRediT authorship contribution statement

Ayataka Fujimoto: Formal analysis, Investigation, Writing – original draft. **Yuji Matsumaru:** Formal analysis, Investigation, Supervision, Validation, Writing – review & editing. **Yosuke Masuda:** Data curation, Formal analysis, Investigation. **Keishiro Sato:** Formal analysis, Investigation. **Keisuke Hatano:** Formal analysis. **Shingo Numoto:** Formal analysis. **Ryuya Hotta:** Formal analysis. **Aiki Marushima:** Formal analysis, Writing – review & editing. **Hisayuki Hosoo:** Formal analysis, Investigation, Resources. **Kota Araki:** Formal analysis, Investigation, Resources. **Tohru Okanishi:** Data curation, Formal analysis, Methodology. **Eiichi Ishikawa:** Supervision, Validation.

Declaration of competing interest

We wish to draw the attention of the Editor to the following facts which may be considered as potential conflicts of interest and to significant financial contributions to this work. We wish to confirm that there are no known conflicts of interest associated with this publication and there has been no significant financial support for this work that could have influenced its outcome except for Yuju Matsumaru (YuM). This research was supported by the Japan Agency for Medical Research and Development (AMED) under grant number JP23he0122011. One author (YuM) is the CEO of E.P. Medical Inc. (Tokyo, Japan).

We confirm that the manuscript has been read and approved by all named authors and that there are no other persons who satisfied the criteria for authorship but are not listed.

We further confirm that the order of authors listed in the manuscript has been approved by all of us.

We confirm that any aspect of the work covered in this manuscript that has involved either experimental animals or human patients has been conducted with the ethical approval of all relevant bodies and that such approvals are acknowledged within the manuscript.

We understand that the first author and corresponding author are the contact for the editorial process (including Editorial Manager and direct communications with the office).

I, Ayataka Fujimoto, am responsible for communicating with the other authors about progress, submissions of revisions and final approval of proofs.

We confirm that we have provided a current, correct email address which is accessible by the Corresponding Author and which has been configured to accept email from Ayataka Fujimoto (afujimotoscienceacademy@gmail.com).

Acknowledgments

We are thankful to all neurological physicians at Seirei Hamamatsu General Hospital for reading eEEG.

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